REMARKS

Applicant respectfully requests reconsideration. Claims 60-62 were previously pending in this application. Claim 60 has been amended to clarify the scope of the claim. Support for this amendment is found in the application at least on page 5, lines 21-28. As a result, claims 60-62 are pending for examination with claim 60 being an independent claim. No new matter has been added.

Rejections under 35 U.S.C. § 112

Claims 60-62 are rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has requested clarification of claim 60 as to whether the UCP antibody is the same entity as the UCP inhibitor and the lysosomal targeted binding peptide. Applicant has amended claim 60 to clarify that the lysosomal UCP inhibitor is a UCP antibody. Because several claims have been combined the term lysosomal targeted binding peptide is redundant and no longer necessary. Support for this amendment is found in the application on page 5, lines 21-28.

Claims 60-62 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant traverses the rejection.

Applicant submits that the Examiner has failed to meet her burden regarding a *prima facie* case of enablement. The test of enablement is whether undue or unreasonable experimentation is required for one of ordinary skill in the art to practice (i.e., make and use) the claimed invention. Thus, based on the specification and the knowledge in the art at the time of filing (i.e., effective filing date), one of ordinary skill is able to make and use the claimed invention without undue experimentation. The experimentation may be complex and still not be undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the

invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive of the issue of enablement. The Examiner appears not to have considered all of the Wands factors, including the nature of the invention and the level of ordinary skill in the art, as set forth under the test of enablement. Applicant submits that a complete analysis of the Wands factors does not support the Examiner's assertion that the claims lack enablement. Although the cited references disclose that there are challenges with intracellular delivery, these references do not disclose that it can not be achieved.

1. The Nature of the Invention

The nature of the invention is related to methods for regulating lysosomal pH by administering a lysosomal UCP inhibitor to a cell. Applicant has presented a description of lysosomal UCP inhibitors and their functions (see page 49, lines 3-26), and a list of commercially available antibodies (see pages 21-22, abridging paragraph), and one of ordinary skill in the art would be able to select an antibody for inhibiting UCP using no more than routine experimentation.

2. The Breadth of the Claims

Applicant asserts that the claims are not overly broad. Applicant has claimed only methods of regulating pH by administering a lysosomal UCP inhibitor that is a UCP antibody to a cell as disclosed in the application.

3. State of the Prior Art

The Examiner has cited Stayton et al. (J. Controlled Release, 65:203-220, 2000), Lobato et al. (Trends in Molecular Med., 9(9):390-396, 2003), Derossi et al. (J. Biol. Chem., 269(14):10444-10450, 1994), Pooga et al. (FASEB J., 12:67-77, 1997), and Elliott et al. (Cell, 88:223-233) to illustrate that the field of *in vivo* polypeptide and/or antibody delivery is still in its infancy and many hurdles remain before it is enabled for *in vivo* therapeutic applications. Applicant addresses each reference individually. Applicant respectfully disagrees with the Examiner's conclusion regarding the cited references.

According to the Examiner, Stayton et al. state that intracellular delivery is a major challenge and that there are several hurdles to the use of antibodies in cancer treatment. Applicant asserts that when Stayton is viewed in its entirety, it discloses a polymer-based approach to manipulating intracellular delivery using biological polymers that circumvent vesicular trafficking pathways by enhancing transport across the endosomal membrane. Stayton also states that "many of the hurdles can be addressed by protein engineering approaches" (see page 205, left hand column, first paragraph). Stayton then demonstrate that despite the discovery that engineered antibody fragments are not necessarily optimized for folding stability, they were successful in using site-directed mutagenesis to manipulate antibody fragments, specifically a single-chain antibody (scFv) that recognizes the CD44 receptor, and "significantly increase the efficiency of refolding and thus provide direct avenues for making the production of antibodies more economical and practical" (see page 205, left hand column, abridging paragraph). Thus Stayton et al. through the use of protein engineering, a technique known to those of skill in the art and requiring no more than routine methods, were successful in increasing the folding stability of an antibody fragment. This improvement in folding stability of an antibody fragment solved one of the challenges disclosed by Stayton in the use of targeting antibodies for the intracellular delivery of therapeutics.

Lobato et al. is cited as disclosing that there are significant challenges to overcome before intrabodies can be useful as therapeutic agents and that new developments are needed to allow their *efficient* delivery and expression for treatment of human diseases (*emphasis added*). Applicants assert that this statement merely recognizes that the delivery of these intrabodies can be improved and does not state that intrabodies cannot be delivered to cells. Lobato disclose that in fact intrabodies have been successfully used to modulate the expression of proteins upregulated in tumors (see page 392, first full paragraph). Lobato further recognizes that virally mediated gene transfer and immunoliposomes are at least two delivery methods available for the delivery of intrabodies (see page 393, left hand column, first full paragraph). Lobato discloses that "*further* development of safe and effective methods of cytosolic delivery of intrabodies should ensure their future successful application *in vivo*" (see page 393, right hand column, first full paragraph) (*emphasis added*). Lobato clearly recognizes that methods are available and practicable for delivery of intrabodies *in vivo*.

Derossi et al. is cited as disclosing that delivery of polypeptides to target cells *in vitro* or *in vivo* is a rate-limiting step for cell targeting and entry for most polypeptides. This statement merely recognizes that the delivery of a polypeptide is the rate-limiting step, i.e. the slowest part, and does not suggest that the polypeptides cannot be delivered. Derossi demonstrates that the Diptheria A toxin and the homoedomain of Antennapedia are both able to translocate across membranes (see page 10449, right hand column). The fact that Derossi suggest that each protein may translocate the membrane by a different mechanism does not detract from the fact that they both are able to translocate across the membrane. Derossi cites two other references Pooga et al. and Elliott et al. Pooga et al. demonstrate that transportan is able to penetrate every cell type they tested in a rapid and efficient way. Elliott et al. demonstrate that the HSV-1 structural protein VP22 has the property of intercellular transport, which is so efficient that following expression in a subpopulation the protein spreads to every cell in a monolayer, where it concentrates in the nucleus and binds chromatin. Both of these references cited by Derossi provide further teachings that other peptides are capable of crossing membranes.

Applicant asserts that the references as discussed above do not provide any reason for one of ordinary skill in the art to doubt that an antibody as claimed in claim 60 is capable of the delivery of a lysosomal UCP inhibitor of the invention to a cell.

4. Level of Ordinary Skill in the Art

For the standard procedures required to practice the claimed invention, the level of skill in the art is high. Applicant maintains that the person of ordinary skill in the art of cell biology would be a PhD. or MD. and would know how to perform the invention using experimental procedures that would be considered routine.

5. The Predictability or Unpredictability of the Art

Applicants respectfully submit that the art cited by the Examiner in support of the contention of unpredictability, does not demonstrate that intracellular delivery can not be done but asserts that there are challenges with using this technique. Applicant reasserts that the cited references as discussed supra, teach that polypeptides and therapeutic agents can be successfully delivered intracellularly, and further that antibodies can be used as a delivery system.

6. The Amount of Direction or Guidance Presented in the Specification

The Examiner asserts that the specification fails to teach a method of regulating lysosomal pH comprising administration of a UCP antibody.

Applicant respectfully disagrees with the Examiner's conclusion, and asserts that the specification teaches the regulation of lysosomal pH. The application discloses on page 48, lines 6-10, that lysosomal pH can be manipulated by manipulating lysosomal UCP expression and activity. If the expression or activity of the UCP is inhibited the lysosome can develop an acidic pH. If active UCP is expressed in the lysosome protons are dissipated and the pH is altered. Therefore, inhibition of lysosomal UCP activity by a UCP antibody would promote the development of an acidic intra-lysosomal environment. Applicant has presented a description of lysosomal UCP inhibitors and their functions (see page 49, lines 3-26), and a list of commercially available antibodies (see pages 21-22, abridging paragraph). Applicant maintains that the person of ordinary skill in the art would know how to perform the invention having in hand Applicant's disclosure.

7. The Presence or Absence of Working Examples

The Examiner asserts that one skilled in the art would not accept on its face the examples in the specification as being correlative or representative of successfully regulating lysosomal pH following the administration of antibodies. Applicants respectfully disagree with the Examiner's conclusion.

With respect to the working examples *Wands* factor, the court in *In re Wright* stated that "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993) *citing In re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicant has provided not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative working examples. Applicant has presented examples that demonstrate the relationship of Fas to UCP and have determined how that relationship affects the fate of a cell. The specification teaches on pages 36 to 37, abridging paragraph, that the relationship between the plasma membrane uncoupling protein (UCP) and cell surface Fas expression is important to the methods of the invention. Applicant has demonstrated that when Fas is engaged, a signal is sent to the cell

instructing the cell to undergo cellular division. The addition of a chemotherapeutic agent changes the signal to instruct the cell to undergo apoptosis (shown in example 1).

Example 9 further demonstrates that drug/apoptotic resistant cells express high levels of intracellular Fas and are protected from death resulting from changes in mitochondrial membrane permeability transitions. The specification teaches that changes in the plasma membrane potential of a cell, such as the lysosomal membrane, provides the ability to control the fate of the cell. Decreasing the plasma membrane potential by inhibiting plasma membrane UCP activity allows the cell to respond to a signal either promoting rapid cell division or causing cell death depending on the signal (see page 12, lines 10-25). The lysosomal membrane potential is referred to as the pressure on the inside of the lysosomal membrane measured relative to the cytoplasm, which is created by the generation and dissipation of charge within the lysosome (see page 46, lines 3-5). The application discloses on page 48, lines 6-10, that lysosomal pH can be manipulated by manipulating lysosomal UCP expression and activity. If the expression or activity of the UCP is inhibited by for example an antibody, the lysosome can develop an acidic pH. If active UCP is expressed in the lysosome protons are dissipated and the pH is altered. Therefore the Examples and the specification adequately teach the regulation of lysosomal pH using an antibody.

8. The Quantity of Experimentation Required

The Examiner asserts that the quantity of experimentation required to practice the invention would require the *de novo* identification of an antibody which specifically binds lysosomal UCP and the determination of appropriate modes of administration of such an antibody, and concludes that undue experimentation is required to practice the invention.

Applicant respectfully disagrees because the specification provides adequate teaching for one of ordinary skill in the art to practice the invention as claimed. Applicant has provided examples of UCP antibodies available commercially to those of ordinary skill in the art (see pages 21-22, abridging paragraph). One of ordinary skill in the art would be capable with no more than routine experimentation to determine the ability of any of these antibodies to bind to a lysosomal UCP using routine techniques such as Western blotting and ELISA assays. The specification also teaches the delivery of such antibodies and as discussed above intracellular delivery has been achieved successfully using various methods including those disclosed in the

specification. Applicant further teaches that inhibition of lysosomal UCP activity, by for example a lysosomal targeted binding peptide such as a UCP antibody, promotes the development of an acidic intra-lysosomal environment, thus altering the pH of the lysosome. Applicant asserts that the specification together with the examples provides sufficient teaching to one of ordinary skill in the art to enable them to practice the claimed invention.

Applicant maintains that full consideration of each and all of the *Wands* factors leads one to the reasonable conclusion that practicing the invention would not require undue experimentation. Applicant asserts that a complete analysis of the Wand's factors does not support the Examiner's assertion that the claims lack enablement because the specification teaches the regulation of lysosomal pH using an antibody.

Accordingly, withdrawal of the rejection of claims 60-62 under 35 U.S.C. § 112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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